ORIGINAL ARTICLE

Comparison of Predictors and Mortality Between Bloodstream Infections Caused by ESBL-Producing *Escherichia coli* and ESBL-Producing *Klebsiella pneumoniae*

Oded Scheuerman, MD;[1,2,3] Vered Schechner, MD;[1,2,3] Yehuda Carmeli, MD;[1,2,3] Belen Gutiérrez-Gutiérrez, MD;[4,5] Esther Calbo, MD;[6] Benito Almirante, MD;[7] Pier-Luigy Viale, MD;[8] Antonio Oliver, MD;[9] Patricia Ruiz-Garbajosa, MD;[10] Oriol Gasch, MD;[11] Monica Gozalo, MD;[12] Johann Pitout, MD;[13] Murat Akova, MD;[14] Carmen Peña, MD;[15] Jose Molina, MD;[16] Alicia Hernández-Torres, MD;[17] Mario Venditti, MD;[18] Nuria Prim, MD;[19] Julia Origüen, MD;[20] German Bou, MD;[21] Evelina Tacconelli, MD;[22] Maria Tumbarello, MD;[23] Axel Hamprecht, MD;[24] Ilias Karaiskos, MD;[25] Cristina de la Calle, MD;[26] Federico Pérez, MD;[27] Mitchell J. Schwaber, MD;[1,2,3] Joaquin Bermejo, MD;[28] Warren Lowman, MD;[29] Po-Ren Hsueh, MD;[30] Carolina Navarro-San Francisco, MD;[31] Robert A. Bonomo, MD;[27,32] David L. Paterson, MD;[33] Alvaro Pascual, MD;[4,5] Jesus Rodríguez-Baño, MD;[4,5] and the REIPI/ESGBIS/INCREMENT investigators[a]

OBJECTIVE. To compare the epidemiology, clinical characteristics, and mortality of patients with bloodstream infections (BSI) caused by extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (ESBL-EC) versus ESBL-producing *Klebsiella pneumoniae* (ESBL-KP) and to examine the differences in clinical characteristics and outcome between BSIs caused by isolates with CTX-M versus other ESBL genotypes.

METHODS. As part of the INCREMENT project, 33 tertiary hospitals in 12 countries retrospectively collected data on adult patients diagnosed with ESBL-EC BSI or ESBL-KP BSI between 2004 and 2013. Risk factors for ESBL-EC versus ESBL-KP BSI and for 30-day mortality were examined by bivariate analysis followed by multivariable logistic regression.

Affiliations: 1. Division of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; 2. National Center for Infection Control, Israel Ministry of Health, Tel Aviv, Israel; 3. Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; 4. Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Seville, Spain; 5. Instituto de Biomedicina de Sevilla, Universidad de Sevilla, Seville, Spain; 6. Hospital Universitari Mútua de Terrassa, Barcelona, Spain; 7. Hospital Universitari Vall d'Hebrón, Barcelona, Spain; 8. Teaching Hospital Policlinico S. Orsola Malpighi, Bologna, Italy; 9. Hospital Universitario Son Espases, Palma de Mallorca, Spain; 10. Hospital Ramón y Cajal, Madrid, Spain; 11. Corporacio Sanitaria Parc Taulí, Sabadell, Barcelona, Spain; 12. Hospital Universitario Marqués de Valdecilla—IDIVAL, Santander, Spain; 13. Department of Pathology and Laboratory Medicine, University of Calgary, Calgary, Alberta, Canada; 14. Hacettepe University School of Medicine, Ankara, Turkey; 15. Hospital Universitari de Bellvitge, Barcelona, Spain; 16. Infectious Diseases, Microbiology and Preventive Medicine, Institute of Biomedicine of Seville (IBiS), University Hospital Virgen del Rocio, CSIC, University of Seville, Seville, Spain; 17. Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; 18. Policlinico Umberto I, University of Rome La Sapienza, Rome, Italy; 19. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 20. Hospital Universitario 12 de Octubre, Madrid, Spain; 21. Complejo Hospitalario Universitario A Coruña, A Coruña, Spain; 22. Universitätsklinikum Tübingen, Tübingen, Germany; 23. Catholic University of the Sacred Heart, Rome, Italy; 24. Institut für Mikrobiologie, Immunologie und Hygiene Universitätsklinikum Köln, Cologne, Germany; 25. Hygeia General Hospital, Athens, Greece; 26. Hospital Clinic, Barcelona, Spain; 27. Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio, United States; 28. Hospital Español, Rosario, Argentina; 29. Wits Donald Gordon Medical Centre, Johannesburg, South Africa; 30. National Taiwan University Hospital, National Taiwan University Hospital College of Medicine, Taipei, Taiwan; 31. Hospital Universitario La Paz, Madrid, Spain; 32. Departments of Medicine, Pharmacology, Biochemistry, Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, Ohio, United States; 33. University of Queensland Centre for Clinical Research, The University of Queensland, Herston, Brisbane, Australia.

[a]Other investigators in the REIPI/ESGBIS/INCREMENT project: J. Guzmán Puche, University General Hospital Attikoni, Greece; M. Souli, Case Western Reserve University School of Medicine, Cleveland Ohio, United States; J. Gálvez, Hospital Universitario Virgen Macarena, Seville, Spain; M. Falcone and A. Russo, Policlinico Umberto I, Rome, Italy; G. Daikos, Laikon General Hospital, Athens, Greece; E. M. Trecarichi and A. R. Losito, Catholic University of the Sacred Heart, Rome, Italy; J. Gómez and E. García-Vázquez, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; E. Iosifidis and E. Roilides, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece; I. Karaiskos, Hygeia General Hospital, Athens, Greece; Y. Doi, University of Pittsburgh, Pittsburgh, Pennsylvania, United States; F. F. Tuon, Hospital da Universidade Federal do Paraná, Paraná, Brazil; J. A. Martínez, L. Morata and A. Soriano, Hospital Clinic, Barcelona, Spain; F. Navarro and B. Mirelis, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; R. San Juan and M. Fernández-Ruiz, Hospital 12 de Octubre, Madrid, Spain; N. Larrosa and M. Puig, Hospital Universitario Vall d'Hebrón, Barcelona, Spain; J. Molina and V. González, Hospital Universitario Virgen del Rocío, Seville, Spain; V. Rucci, Hospital Español, Rosario, Argentina; E. Ruiz de Gopegui and C. I. Marinescu, Hospital Universitario Son Espases, Palma de Mallorca, Spain; M. C. Fariñas, M. E. Cano, and M. Gozalo, Hospital Universitario Marqués de Valdecilla-IDIVAL, Santander, Spain; J. R. Paño-Pardo and Marta Mora-Rillo, Hospital Universitario La Paz-IDIPAZ, Madrid, Spain; S. Gómez-Zorrilla and F. Tubau, Hospital de Bellvitge, Barcelona, Spain; S. Pournaras, A. Tsakris, and O. Zarkotou, University of Athens, Athens, Greece; Ö. K. Azap, Baskent University, Ankara, Turkey; M. Souli, A. Antoniadou, and G. Poulakou, University General Hospital Attikon, Chiadiri, Greece; D. Virmani, University of Calgary, Calgary, Canada; Á. Cano and J. Guzmán-Puche, Hospital Universitario Reina Sofía-IMIBIC, Córdoba, Spain; Ö. Helvaci and A. O. Sahin, Hacettepe University, Ankara, Turkey; V. Pintado and R. Cantón, Hospital Ramón y Cajal, Madrid, Spain; M. Bartoletti and M. Giannella, Teaching Hospital Policlinico S. Orsola Malpighi, Bologna, Italy; S. Peter, Tübingen University Hospital, Tübingen, Germany; C. Badia and M. Xercavins, Hospital Universitario Mútua de Terrassa, Terrassa, Spain; D. Fontanals and E. Jové, Hospital Parc Taulí, Sabadell, Spain.

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RESULTS. The study included 909 patients: 687 with ESBL-EC BSI and 222 with ESBL-KP BSI. ESBL genotype by polymerase chain reaction amplification of 286 isolates was available. ESBL-KP BSI was associated with intensive care unit admission, cardiovascular and neurological comorbidities, length of stay to bacteremia >14 days from admission, and a nonurinary source. Overall, 30-day mortality was significantly higher in patients with ESBL-KP BSI than ESBL-EC BSI (33.7% vs 17.4%; odds ratio, 1.64; $P = .016$). CTX-M was the most prevalent ESBL subtype identified (218 of 286 polymerase chain reaction-tested isolates, 76%). No differences in clinical characteristics or in mortality between CTX-M and non–CTX-M ESBLs were detected.

CONCLUSIONS. Clinical characteristics and risk of mortality differ significantly between ESBL-EC and ESBL-KP BSI. Therefore, all ESBL-producing Enterobacteriaceae should not be considered a homogeneous group. No differences in outcomes between genotypes were detected.

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The spread of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-E) is a growing public health threat worldwide.[1] A 2012 study from 72 hospitals in the United States reported that 16% of *Klebsiella pneumoniae* and 11.9% of *Escherichia coli* isolates were ESBL producers.[1] Much higher proportions were found in other populations,[2] with variation between countries and between hospitals. The limited antibiotic treatment options and adverse clinical outcomes of infections caused by ESBL-E have raised major concerns among clinicians and infection control services.[3]

In the 1980s and 1990s, *K. pneumoniae* was the predominant ESBL-E causing nosocomial outbreaks, and TEM and SHV were the main β-lactamases involved.[4,5] In recent decades, *E. coli* has surpassed *K. pneumoniae,* and the most common β-lactamase is CTX-M.[6]

Most previous studies that examined the epidemiology and outcome of infections caused by ESBL-producing organisms often combined different Enterobacteriaceae to one group assuming homogeneity; moreover, differences in outcomes between ESBL genotypes have not been considered.[4,7] However, this may not be the case. For example, unlike ESBL-producing *K. pneumoniae* (ESBL-KP), ESBL-producing *E. coli* (ESBL-EC) is common in community-acquired infections.[6] ESBL-EC has less predilection for hospital transmission than other ESBL-producing species, which has led the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) to recommend contact precautions for patients colonized with all ESBL-E except ESBL-EC.[8]

In this study, our aims were twofold: (1) to compare the epidemiology, clinical characteristics, and mortality of patients with bloodstream infections (BSIs) caused by ESBL-EC versus ESBL-KP; and (2) to examine the differences in clinical characteristics and outcome between BSIs caused by isolates with CTX-M versus other ESBL genotypes.

METHODS

Study Design and Patients

This analysis was part of the INCREMENT project, a retrospective cohort study designed to evaluate the epidemiology, clinical features, treatment efficacy, and prognosis of clinically significant BSI due to ESBL- or carbapenemase-producing Enterobacteriaceae.[9] In total, 33 tertiary-care hospitals in 12 countries participated in the project. For the present study, we included all adult patients (age > 18 years) with clinically significant, monomicrobial BSIs caused by ESBL-EC or ESBL-KP from January 2004 through December 2013.

Variables and Definitions

Patient data were collected from hospital medical charts and included the following: demographic characteristics, ward type, site of acquisition (nosocomial, healthcare-associated or community), length of stay to bacteremia, source of infection (eg, urinary, biliary), comorbidities (individually and by Charlson score, dichotomized as ≤2 or > 2),[10] severity of underlying illness as measured by McCabe classification,[11] severity of BSI (presence of severe sepsis or septic shock and Pitt bacteremia score dichotomized as ≤4 or > 4),[12] organism and resistance genotype, and 30-day mortality (calculated from the day of the first positive blood culture was taken). For patients who were no longer hospitalized at 30 days, we determined mortality by telephoning patients or their relatives and by consulting mortality registers.

Infections were defined as nosocomial if symptoms began > 48 hours after hospital admission or within 48 hours of hospital discharge. Infections were defined as healthcare-associated if they were not nosocomial and if, in the previous 3 months, the patient was hospitalized in an acute-care hospital, long-term care facility or day hospital, had undergone dialysis, surgery or other invasive procedure, or received specialized home care. Patients who were neither nosocomial nor healthcare associated were considered strictly community acquired. The definitions of the Centers for Disease Control and Prevention (CDC) for nosocomial infections were used to classify the primary source of infection.[13] Antimicrobial therapy was considered appropriate when including at least 1 drug active in vitro against the causative bacteria.

Laboratory Methods

Enterobacteriaceae strains were identified using standard microbiological techniques in each participating center. ESBL

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production and susceptibility to given antibiotics were screened and confirmed according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[14] For some isolates, the ESBL genes had been characterized by polymerase chain reaction (PCR)[8] according to the needs of the local laboratories; no criteria were specified for the selection of the isolates. For secondary BSI, the source (eg, urine, wound) did not need to be microbiologically confirmed if enough clinical criteria were present.

Statistical Analysis

Risk factors for ESBL-EC versus ESBL-KP BSI and for death were initially examined by bivariate analysis. Categorical variables were compared using the χ^2 test, and continuous variables were compered using the t test. Variables with $P < 0.10$ were included in a multivariable logistic model. In addition, we decided a priori to include age and sex in the multivariable model. In the multivariate logistic model, $P < 0.05$ was considered statistically significant.

SPSS version 22.0 software (SPSS, Chicago, IL) and SAS version 9.4 software (SAS Institute, Cary, NC) were used for this analysis.

Ethics

The Spanish Agency of Medicines and the Hospital Universitario Virgen Macarena Institutional Review Board approved the INCREMENT project. The need for written informed consent was waived. Approvals were also obtained from the institutional review boards of all participating centers.

RESULTS

Our sample included 909 patients: 687 (75%) with ESBL-EC and 222 (25%) with ESBL-KP BSI. The contributing institutes and the number of cases contributed by each center are summarized in Supplementary Table 1. The median age was 69 years (interquartile range [IQR], 56–79 years), and 55% of the patients were male. Only 149 patients (16%) had a strictly community-acquired infection. The median length of stay to bacteremia from admission was 1 day (IQR, 0–11 days). The urinary tract was the most common source of BSI (397 patients, 44%), followed by intra-abdominal infection (106, 12%) and the biliary system (104, 11%). Moreover, 44% of patients had a high Charlson comorbidity index (>2); 12.5% had a high Pitt bacteremia score (>4); and 35.5% developed severe sepsis or septic shock.

Risk Factors for BSI Caused by ESBL-EC Versus ESBL-KP

Table 1 compares epidemiological and clinical characteristics between patients with ESBL-EC BSI and ESBL-KP BSI. In bivariate analysis, patients with ESBL-KP were more likely to have cardiovascular, neurologic, or renal disease, and they were more likely to be in the ICU at the time of BSI diagnosis, to have a nosocomial BSI, and to have developed bacteremia >14 days after admission. A urinary source was more common in patients with ESBL-EC BSI. In the multivariable model, ESBL-KP BSI was independently associated with ICU admission, cardiovascular disease, neurological disease, later onset of bacteremia, and a nonurinary source.

In a subgroup analysis of 423 patients with nosocomial BSI, the same 5 risk factors were significant in a multivariable model (data not shown). No significant risk factors were found for patients with healthcare-associated community acquisition. Subgroup analysis of patients with strict community acquisition was not done due to small number of patients (21 patients with ESBL-KP).

Thirty-Day Mortality Following ESBL-EC Versus ESBL-KP BSI

The 30-day mortality rate was higher among patients with ESBL-KP BSI than with ESBL-EC BSI (33.7% vs 17.4%). Differences in mortality risk factors between ESBL-EC and ESBL-KP BSI are summarized in Table 2A and 2B. Septic shock/severe sepsis, bad prognosis according to McCabe classification, and inappropriate targeted therapy were risk factors for mortality in both ESBL-EC and ESBL-KP. Other risk factors for mortality, age and nonurinary source, were significant only in ESBL-EC. However, the odds ratios (ORs) exhibited a similar trend in ESBL-KP but did not reach statistical significance due to the smaller cohort. ESBL-KP remained an independent predictor of 30-day mortality (OR, 1.64; 95% confidence interval [CI], 1.1–2.5). In the healthcare-associated community-acquisition subgroup, mortality rates were also significantly higher in ESBL-KP versus ESBL-EC (27% vs 14%; $P = .0125$).

Differences in Clinical Characteristics and Outcome by ESBL Genotype

A total of 286 bacterial isolates (218 EC and 68 KP) underwent PCR amplification of *bla* ESBL genes. No significant differences were found between patients whose isolates had and had not their ESBL genes characterized in terms of demographics, underlying conditions, bacterial species, sources of infection, severity of infection, or mortality (data not shown). CTX-M was the most prevalent ESBL subtype identified (218, 76%), both in *E. coli* (78%) and in *K. pneumoniae* (69%). The other ESBL genotypes present in our sample were SHV and TEM (22% of *E. coli* and 31% of *K. pneumoniae*). Table 3 compares clinical characteristics and outcomes in patients with BSI caused by bacteria producing CTX-M versus other ESBL enzymes. In bivariate analysis, non–CTX-M was significantly associated with pulmonary, cardiovascular, neurological, and connective tissue disease and with total Charlson score >2. We did not find significant differences in clinical severity of the BSI, site of acquisition, or mortality rate between CTX-M and non–CTX-M ESBLs.

Of the 68 patients, 13 (19%) with non–CTX-M were strictly community acquired compared with 30 of 218 patients with

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TABLE 1. Demographic and Clinical Characteristics of Patients With ESBL-EC and ESBL-KP Bloodstream Infection[a]

Covariate		ESBL-EC (N = 687), No. (%)	ESBL-KP (N = 222), No. (%)	Crude OR	*P* Value	OR Multivariate (95% CI)[b]	*P* Value
Demographics							
Sex	Male	370 (54)	134 (60)	1.305	.09		
	Female	317 (46)	88 (40)				
Age, medan y (IQR)		69 (56–79)	70 (59–79)	1.003	.509		
Site of acquisition							
Nosocomial		284 (42)	139 (63)	2.349	<.001	1.391 (0.929–2.081)	.109
Community		383 (58)	80 (37)				
	Strictly community	128 (36)	21 (27)		.12		
	Community-healthcare- associated	230 (64)	58 (73)				
Epidemiological parameters							
Source	Urinary tract	327 (48)	70 (32)	0.507	<.001	0.596 (0.416–0.854)	.005
	Other	360 (52)	152 (68)				
Ward type	Emergency dept.	219 (32)	21 (15)				
	Medical ward	316 (46)	97 (45)				
	Surgical ward	92 (14)	39 (18)				
	ICU	56 (8)	47 (22)	3.151	<.001	2.303 (1.45–3.65)	<.001
	Unknown	22					
LOS to bacteremia	0–14 days	575 (84)	150 (68)	2.464	<.001	1.703 (1.1–2.639)	.017
	>14 days	112 (16)	72 (32)				
Clinical characteristics and comorbidity							
Cardiovascular disease		137 (20)	81 (36.5)	2.306	<.001	2.187 (1.527–3.13)	<.001
Neurologic disease		83 (12)	41 (18)	1.623	.02	1.618 (1.032–2.537)	.036
Pulmonary disease		115 (17)	45 (20)		.25		
Renal disease		127 (19)	58 (27)	1.559	.015		
Liver disease		89 (13)	25 (11)		.43		
Inflammatory bowel disease		37 (5.6)	5 (2)	0.398	.049		
Malignancy		262 (40)	80 (37)		.526		
HIV positive		14 (2)	2 (0.9)		.26		
Charlson comorbidity score	≤2	286 (41.6)	107 (48)	1.305	.086		
	> 2	401 (58)	115 (52)				
McCabe classification	Nonfatal	337 (51)	109 (51)		.867		
	Death w/i 1 y[c]	226 (34)	77 (36)				
	Death w/i 5 y[c]	97 (15)	29 (13)				
Pitt score	≤4	657 (96)	202 (91)	2.168	.008		
	>4	30 (4)	20 (9)				
Severe sepsis/septic shock		227 (34)	96 (44)	1.54	.007		

NOTE. ESBL, extended-spectrum β-lactamase; EC, *Escherichia coli*; KP, *Klebsiella pneumoniae*; IQR, interquartile range; OR, odds ratio; ICU, intensive care unit; HIV, human immunodeficiency virus; LOS, length of stay.

[a]Percentage of persons with known data.

[b]Odds ratio (OR) is for ESBL-KP infection.

[c]Death expected within 1 year or 5 years, as indicated.

CTX-M (14%; *P* = .28). In addition, 10 patients (n = 13) were from a single center, which might reflect local epidemiology and not a general trend.

DISCUSSION

In this large cohort of patients with ESBL-E BSI, we found differences between patient characteristics, clinical presentation, and outcome, depending on whether the causative organism was for ESBL-EC or ESBL-KP. Bacteremia due to ESBL-KP was more often of nonurinary origin, occurred later during hospitalization, was associated with comorbidities (cardiovascular and neurological) and had a more severe clinical presentation. Bacteremia due to ESBL-EC tended to occur more often upon admission (community onset) and to have a urinary source. Our results are in accordance with a previous study by Freeman et al[15] who demonstrated differences in risk profiles and clinical characteristics between patients with ESBL-EC BSI (eg, community-acquired infections) and patients with ESBL-KP BSI (eg, ICU admission).[15]

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Gram-negative bacillary sepsis with shock has a mortality rate of 12%–38%.[2,16] In our cohort, the 30-day mortality rate was 21.4% and was significantly higher for ESBL-KP BSI (33.7%) than for ESBL-EC BSI (17.4%). We found that bacterial species is among the most important determinants of the risk for mortality. A study conducted in Finland likewise found higher 28-day mortality in patients with nosocomial BSI caused by ESBL-KP (28.0%) than by ESBL-EC (14.8%).[2] In contrast, Leistner et al[16] did not find a difference in in-hospital mortality between BSI caused by ESBL-KP and ESBL-EC, although they did find significantly higher mortality with ESBL-negative KP than with ESBL-negative EC.

TABLE 2. Risk Factors for 30-Day Mortality in Patients With ESBL-EC (TABLE 2A) and ESBL-KP (TABLE 2B) Bloodstream Infection by Univariate and Multivariate Analyses

TABLE 2A

Parameter		No Mortality (n = 567), No. (%)	30-Day Mortality (n = 120), No. (%)	Crude OR	*P* Value	OR Multivariate (95% CI)[a]	*P* Value
Male sex		303 (53)	67 (56)	1.101	.633	1.08 (2.309–0.742)	.352
Age, median y (IQR)		68 (55–79)	73 (60–79)	1.016	.012	1.042 (1.020–1.064)	<.001
Site of acquisition	Nosocomial	221 (40)	63 (55)	1.820	.003	1.160 (0.586–2.296)	.671
	Community	332 (60)	52 (45)				
Source	Urine	295 (52)	32 (27)	0.330	<.001	0.316 (0.165–0.608)	<.001
	Other	272 (48)	88 (73)				
Appropriate empirical therapy	No	257 (45)	75 (62)	0.497	<.001	0.841 (0.422–1.677)	.623
	Yes	310 (55)	45 (33)				
Appropriate targeted therapy	No	69 (12)	53 (44)	0.175	<.001	0.202 (0.093–0.439)	<.001
	Yes	498 (88)	67 (56)				
Length of stay to bacteremia	0–14 days	483 (85)	92 (77)	1.75	.022	1.384 (0.609–3.145)	.438
	>14 days	84 (15)	28 (23)				
ICU		37 (7)	19 (16)	2.706	<.001	2.188 (0.923–5.187)	.075
Cardiovascular disease		106 (19)	32 (27)	1.581	.048		
Neurologic disease		65 (11)	18 (15)	1.363	.280		
Pulmonary disease		82 (15)	33 (29)	2.331	<.001		
Diabetes mellitus		179 (32)	43 (37)	1.267	.265		
Connective tissue disorder		16 (3)	4 (4)	1.245	.699		
Inflammatory bowel disease		28 (5)	9 (8)	1.638	.211		
Liver disease		71 (13)	18 (16)	1.294	.367		
Renal disease		102 (19)	25 (22)	1.212	.444		
Malignancy		204 (37)	58 (51)	1.778	.005	1.047 (0.514–2.132)	.898
HIV positive		12 (2)	2 (2)	0.808	.782		
Charlson comorbidity index	≤2	347 (61)	54 (45)	1.928	.001	1.275 (0.694–2.343)	.434
	>2	220 (39)	66 (55)				
McCabe classification	Nonfatal	305 (56)	32 (28)		<.001		.001
	5 years	182 (33)	44 (38)			1.950 (0.974–3.903)	
	1 year	58 (11)	39 (34)			5.501 (2.185–13.849)	
Global Pitt score	≤4	559 (99)	98 (82)	15.686	<.001	5.214 (1.377–19.740)	.151
	>4	8 (1)	22 (18)				
Severe sepsis/shock		140 (26)	87 (74)	8.431	<.001	6.724 (3.740–12.090)	<.001

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TABLE 2B.

Parameter		No Mortality (n = 147), No. (%)	30-Day Mortality (n = 75), No. (%)	Crude OR	*P* Value	OR Multivariate (95% CI)[a]	*P* Value
Male sex		90 (61)	44 (59%)	0.899	.712	0.731 (0.661–1.615)	.424
Age, median y (IQR)		71 (55–79)	68 (61–76)	1.003	.785	1.010 (0.983–1.037)	.481
Site of acquisition	Nosocomial	83 (58)	56 (75)	2.16	.013	1.292 (0.552–3.028)	.555
	Community	61 (42)	19 (25)				
Source	Urine	55 (37)	15 (20)	0.43	.008	0.609 (0.254–1.462)	.267
	Other	92 (63)	60 (80)				
Appropriate Empirical Therapy	No	75 (51)	37 (49)	1.07	.81		
	Yes	72 (49)	38 (51)				
Appropriate Targeted Therapy	No	25 (17)	23 (31)	0.46	.019	0.345 (0.145–0.822)	.016
	Yes	122 (83)	52 (69)				
Length of stay to bacteraemia	0–14 d	104 (71)	46 (61)	1.52	.16		
	>14 d	43 (29)	29 (39)				
ICU		20 (14)	27 (37)	3.55	<.001	1.425 (0.510–3.980)	.499
Cardiovascular disease		52 (35)	29 (39)	1.15	.629		
Neurologic disease		27 (18)	14 (18)	1.02	.956		
Pulmonary disease		30 (21)	15 (20)	0.95	.88		
Diabetes mellitus		50 (35)	31 (42)	1.402	.25		
Connective tissue disorder		4 (3)	3 (4)	1.44	.69		
Inflammatory bowel disease		4 (3)	1 (1)	0.48	.66		
Liver disease		17 (12)	8 (11)	0.899	.815		
Renal disease		34 (24)	24 (33)	1.57	.153		
Malignancy		57 (40)	23 (32)	0.686	.215		
HIV positive		1 (1)	1 (1)	1.959	.630		
Charlson comorbidity index	≤2	82 (56)	33 (44)	1.606	.096	1.389 (0.614–3.140)	.430
	>2	65 (44)	42 (56)				
McCabe classification	Nonfatal	82 (57)	27 (37)		<.001		.022
	5 years	10 (7)	19 (26)			1.553 (0.640–3.770)	
	1 year	50 (37)	27 (37)			5.567 (1.638–18.927)	
Global Pitt score	≤4	143 (97)	59 (79)	9.69	<.001	3.949 (0.983–15.870)	.053
	>4	4 (3)	16 (21)				
Severe sepsis/shock		42 (30)	54 (72)	6.06	<.001	4.270 (1.952–9.339)	<.001

NOTE. ESBL, extended-spectrum β-lactamase; EC, *Escherichia coli*; KP, *Klebsiella pneumoniae*; OR, odds ratio; ICU, intensive care unit; HIV, human immunodeficiency virus.
[a]OR is for ESBL-KP infection.

Here, CTX-M was the most prevalent type of ESBL in our sample, as in other studies.[16] There was no significant association between the type of ESBL (CTX-M vs non–CTX-M) and the organism or between the type of ESBL and whether the infection was nosocomial. These findings are consistent with previous data.[17]

Epidemiologically, it has been suggested that CTM-X β-lactamase has higher rates of community transmission and an association with *E. coli*.[17] Our data support studies indicating that CTX-M is also prevalent in ESBL-KP.[18] We found that non–CTX-M was associated with pulmonary, cardiovascular, neurological, and connective-tissue diseases.

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TABLE 3. Epidemiological and Clinical Characteristics of Patients With ESBL-E Blood Stream Infection Characterized by PCR Amplification of *bla* ESBL Genes: CTX-M Versus Non–CTX-M

Characteristics	ESBL-E by PCR (N = 286), No. (%)		
	CTX-M (n = 218)	Non–CTX-M (n = 68)	*P* Value
Organism			
Escherichia coli	171 (78)	47 (69)	.115
Klebsiella pneumoniae	47 (22)	21 (31)	
Male sex	119 (55)	99 (48)	.382
Nosocomial acquisition	110 (50)	34 (50)	.994
Urinobiliary source	107 (49)	36 (53)	.617
Department			
ICU	19 (9)	7 (11)	.565
Medical and surgical	150 (69)	44 (73)	
Emergency	49 (23)	11 (17)	
Comorbidities			
Diabetes mellitus	73 (33)	31 (45)	.084
Pulmonary disease	42 (19)	25 (37)	.003
Cardiovascular disease	49 (21)	28 (41)	.001
Connective tissue disorder	5 (2)	7 (11)	.003
Inflammatory bowel disease	13 (6)	5 (7)	.804
Liver disease	27 (12)	12 (17)	.339
Kidney disease	38 (17)	18 (27)	.095
Malignancy	101 (46)	30 (44)	.782
Neurological disease	27 (12)	18 (26)	.008
HIV positive	7 (3)	3 (4)	.621
Charlson score			
≤2	129 (59)	26 (38)	.002
>2	89 (41)	42 (62)	
Length of Stay to Bacteremia			
0–14 days	163 (75)	52 (76)	.835
>14 days	55 (25)	16 (24)	
Severe sepsis/shock	81 (37)	26 (39)	.793
Total Pitt score			
≤4	205 (94)	60 (88)	.149
>4	13 (6)	8 (12)	
Mortality	48 (22)	15 (22)	.93

NOTE. ESBL-E, extended-spectrum β-lactamase-producing Enterobactericeae; KP, *Klebsiella pneumoniae*; OR, odds ratio; ICU, intensive care unit; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

It was also associated with total Charlson score >2, which may suggest that these patients' infections were more healthcare associated. We conclude that, today, both ESBL-EC and ESBL-KP contain the CTX-M and non–CTX-M subtypes and that infections with all ESBL genotypes can occur in the community and in the hospital settings.

Our study has several strengths. The data were acquired from different hospitals in several countries, and the sample size was large. However, this study also has several limitations. The retrospective design of the study could be subject to information bias. However, we believe that the large number of patients included at least partly overcomes this problem. We analyzed the data from all countries together, but the epidemiology of ESBL genotypes may vary between countries. The ESBL genes were only characterized by PCR in a subgroup of isolates; however, the features of these patients were similar to those for which the ESBL gene were not studied.

In conclusion, the epidemiology, clinical characteristics, and risk of mortality differ significantly between ESBL-EC and ESBL-KP, and these factors do not differ by ESBL genotype. Therefore, we recommend that ESBL-E should not be considered a homogenous group. In addition to the different epidemiology of the bacteria, the clinical course differs; thus, different treatment options may be needed. Further studies should focus on individual bacteria and not on ESBL-E as a group.

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Address correspondence to O. Scheuerman, MD, Division of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center Tel Aviv and Schneider Children's Medical Center of Israel, Petach Tikva 4920235, Israel (odedshv@clalit.org.il).

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2018.63.

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